Institution: University of Nottingham

Unit of Assessment: 15 General Engineering

Title of case study: Use of biomechanical modelling to develop and commercialise an artificial spinal implant

1. Summary of the impact

Research into the biomechanics of intervertebral discs at the University of Nottingham has made a significant contribution to the development of two medical implants (Cadisc®- L and Cadisc®-C) by Ranier Technology Ltd. 226 patients (90% outside the UK) have had this treatment, which has outperformed the alternatives by 34% in measured outcomes of reducing patient disability (ODI), pain and quality of life (QALY). Consequently, Cadisc® now accounts for all of Ranier's business. The company has expanded its workforce to 35 people and has attracted external investment of £13M to perform clinical trials and manufacture the product.

2. Underpinning research

The discs of the lumbar and cervical spine are subject to degenerative changes caused by ageing and the stresses of day-to-day life. The resulting loss in disc height and flexibility and reduced ability to absorb shock can lead to pain or even tearing or rupturing of the disc. As one of the most common causes of back pain, the Chartered Society of Physiotherapy estimates that: disc degeneration is estimated to cost the UK economy alone over £12Bn a year; nearly 2 million people worldwide are treated for spinal disc defects annually and 50% require some structure to be inserted or implanted; over 7 million work days were lost in the UK from back pain related illness in 2011 and; back pain is the second most common cause of illness and time off work [4.1].

It is in this area that Dr Donal McNally (Reader in Bioengineering, University of Nottingham, 2001-current) has focused an important part of his research. His work has primarily investigated the internal mechanical behaviour of the intervertebral disc and load transfer between it and the adjacent vertebrae.

Between 2002 and 2009 McNally and his team studied the mechanics of the intervertebral disc (including the permeability of the cartilage end plate) and variations of load patterns in the vertebra after disc implantation. This was done by developing finite element models of natural and artificial discs [2.1, 2.4]. The researchers observed an altered stress pattern in the vertebrae adjacent to implanted segments and found that the use of smaller-size implants and presence of voids at the interface caused localised stress concentration in the endplate and adjacent spongy bone. The research [2.4] supported the hypothesis that conventional implants fail to restore normal loading patters in the vertebral body and that localised high-stress regions could be a source of pain and the reason for the low success rate of traditional total disc replacements. Other studies [2.2] focused on examining and quantifying the loading and load transfer between the intervertebral discs and the adjacent vertebrae.

Work on Cadisc® began in 2002, when medical device development company Ranier Technology began sponsoring three PhD students and a postdoctoral researcher at the University of Nottingham, who – led by McNally – have contributed key research to Cadisc®'s development. An *in vitro* investigation of the effect of implantation of Cadisc®-L (for the lumbar spine), using frozen human lumbar spines, showed a reduction in axial stiffness while maintaining disc height and flexion stiffness – all conducive to preserving the biomechanics of an implanted spinal motion segment [2.3]. The research also contributed to the development of Cadisc® by: investigating the design and performance of surgical instrumentation; validating the manufacturing process; modelling the performance of Cadisc®-C for the cervical spine [2.5]; analysis of load transmission from vertebrae to implant [6]; and confirmation of the biofidelic performance of the device.

The work is highly multidisciplinary and has involved collaboration with: spine surgeons (Arun, Freeman and Mullholland at Nottingham, Fairbank and Meir at Oxford) to understand better the surgical needs specific to spine surgery and ease of operation; orthopaedic surgeon (Scammel at

Nottingham), to appreciate the general surgical situation; physicists (Gowland and Cox at Nottingham) to aid with imaging and measurement techniques to evaluate the pre and post-surgery conditions; physiologists (Jones and Urban at Oxford) to understand the human physiology aspects.

The award of the International Society for the Study of the Lumbar Spine (ISSLS) Prize – one of the most prestigious awards in spinal research – in two of three categories in 2009 demonstrates the internationally leading quality of the research produced by McNally and his group [2.5, 2.6].

3. References to the research

References *(Items marked with an asterisk indicate 3 most significant papers);*

2.1. Riches, P.E. and McNally, D.S., 2005, A one-dimensional theoretical prediction of the effect of reduced end-plate permeability on the mechanics of the invertebral disc, *Proceedings of the Institute of Mechanical Engineers, Part H – Journal of Engineering in Medicine*, 219(H5), 329-335 DOI: 10.1243/095441105X34365

2.2. McNally, D.S., 2002, The objectives for the mechanical evaluation of spinal instrumentation have changed, *European Spine Journal*, 11, 179-185 DOI: 10.1007/s00586-002-0435-5

2.3. McNally, D., Naylor, J. and Johnson, S., 2012, An in vitro biomechanical comparison of Cadisc®-L with natural lumbar discs in axial compression and sagittal flexion, *European Spine Journal*, 21(5) 612-617 DOI: 10.1007/s00586-012-2249-4

2.4. *Palissery, V., Mulholland, R.C.M. and McNally, D.S., 2009, The implications of stress patterns in the vertebral body under axial support of an artificial implant, *Medical Engineering and Physics*, 31, 833-837 DOI: 10.1016/j.medengphy.2009.03.010

2.5. *Meir, A., Fairbank, J.C.T., Jones, D.A., McNally, D.S. and Urban J.P.G., 2007, High pressures and asymmetrical stresses in the scoliotic disc in the absence of muscle loading, *Scoliosis*, 2 (4) DOI: 10.1186/1748-7161-2-4

2.6.*Arun, R., Freeman, B.J.C., Scammel, B.E., McNally, D.S., Cox, E. and Gowland, P., 2009, What influence does sustained mechanical load have on diffusion in the human intervertebral discs? An in-vivo study using serial post-contrast magnetic resonance imaging, *Spine*, 34(21), 2324-2337 (2009 ISSLS Prize winner) DOI: 10.1097/BRS.0b013e3181b4df92, copy available on request.

4. Details of the impact

The underpinning research validates the biomedical function of the Cadisc® implants, which underwent clinical trials on 30 patients from October 2009 to June 2010 [4.2] and has since led to the impacts described below.

Patient health benefits

The research has led to the development of two products that are specifically designed to treat patients suffering from degenerative disc disease – Cadisc®-L, which mimics the biomechanical properties of the natural lumbar disc, and Cadisc®-C, which does the same for the natural cervical disc. Based on the research insights into the mechanical loading on spinal discs and the transfer of fluid, Cadisc® (see Figure 1) is designed to replicate the behaviour of a real spinal disc and hence give better results in terms of pain relief, mobility and quality of life to patients soon after surgery. It is unique in that it does not have a metal endplate and therefore conforms to vertebral anatomy better than conventional implants [4.3].

Figure 1: Cadisc device

The graph below left shows the improvement in Quality Adjusted Life Years (QALY, a standard measure of disease burden including both quality and quantity of life) in the 24 months after

patients received the product, in comparison to alternative treatments available. QALY accrual rate for Cadisc® is 0.7 over 12 months, which is approximately twice that of conventional disc replacements and three times that of spinal fusion, the current "Gold Standard" of care [4.4].

In the UK the National Institute for Health and Care Excellence (NICE) values 1 QALY at £20k to £30k [4.4]. Using this methodology, the intervention already brings a value of around £30k to £45k over the first two years after the intervention per patient.

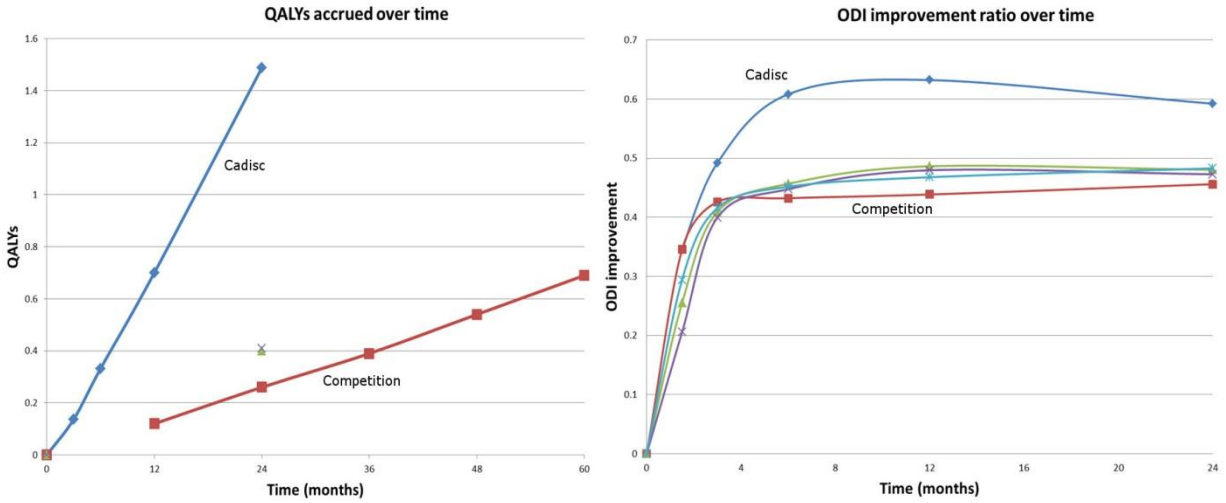

Figure 2: Performance of Cadisc® against competition against QALY's and ODI over time [4.4, 4.6]

Under the Oswestry Disability Index (ODI), one of the principal condition-specific outcome measures used in the management of spinal disorders, Cadisc® has shown a 33% performance improvement compared to competitor products and treatments (see Figure 2 right) [4.5, 4.6].

Between October 2009 and the end of July 2013, 226 patients received these implants; the operative success rate was 100% [4.3].

In 2011, after the clinical trials for Cadisc®-L, Dick Zeilstra, the trial's principal investigator, highlighted the enormous significance of the discs for patient well-being: "Over 80% of patients experienced a clinically significant improvement in Oswestry Disability Index (ODI) scores and there was an average improvement in ODI scores of 63% at 12 months; this compares with an average improvement of 47% in studies of other disc prostheses. Patients also experienced remarkable improvement in quality of life, with Cadisc®-L patients accruing 0.7 of a Quality Adjusted Life Year (QALY) at 12 months. In recently published trials, competitor products demonstrated a mean accrual of 0.14 of a QALY at 12 months and 0.41 at 24 months." [4.5]

The biomechanical advantages of Cadisc® and its ability to mimic the natural disc, informed by UoN research, have been commended by Dr. Hamid Afshar, one of the leading surgeons specialising in this area: "The Cadisc® concept is very unique – a single block disc with no metal components which offers biomechanics similar to the natural disc. Conceptually, it's the ideal solution for the spine. Aside from the biomechanical advantages, the Cadisc® also offers MR and CT imaging compatibility which allows clear visualisation of the adjacent skeletal anatomy and neural tissues. Having nearly 10 years of product development and testing provides surgeons the reassurance that the device will meet the mechanical and functional demands of the spine. The Cadisc® technology has helped patients become pain free and enable them to return to work. In particular, It gives young patients (20-50 years) the opportunity to return to a more active, pain-free lifestyle" [4.7].

Commercial benefits

The research directly contributed to the development and sales of Ranier's two flagship products, Cadisc®-L and Cadisc®-C. £8M of third-party investment was secured (from Alliance Trust Equity

Partners (ATEP) and First Ventures) to fund the clinical testing and European launch in February 2008 [4.8] followed by a further injection of £5M in 2010 by the same companies [4.3, 4.9]. Both products, along with their associated surgical instruments, have been successful in gaining CE marks and have been sold commercially throughout Europe since 2009. An application for an IDE clinical study was submitted to the US Food and Drug Administration (FDA) on June 27th 2011 with a view to marketing the devices in the USA and is pursuing further funding to enable full scale clinical trials to obtain full FDA approval. Distribution contracts were signed in early 2013 to cover the supply of products to the surgical community in South Africa, Australia and New Zealand [4.10 a&b].

The research has transformed Cambridge-based Ranier Technology from a small medical device development company into the only UK manufacturer of total disc replacements. Cadisc® now accounts for all of the company's business. It has gained international reach, exporting 90% of its production, mainly to Germany. Since 2008 its workforce has grown to 35, and its turnover has increased by more than 80% between 2008 and 2013 [4.3].

5. Sources to corroborate the impact

4.1 http://www.csp.org.uk/documents/impact-nhs-reforms-musculoskeletal-physiotherapy-health-social-care-bill-lords-report-stag pdf available on file.

4.2 http://clinicaltrials.gov/ct2/show/NCT00949936?term=Cadisc®+Ranier&rank=1

4.3 Dr Geoffrey Andrews, Director, Ranier Technologies Ltd. (letter dated 22nd August 2013)

4.4 Ian Quirk, Cadisc®™ EU Clinical Trials Current Status, Presentation to the scientific advisory board of Ranier Technologies, January 2013. Copy available on request.

4.5 http://www.cambridgenetwork.co.uk/news/ranier-announces-results-of-its-Cadisc®-l-lumbar-disc/

4.6 Quirk, I, Bertagnoli, R, Conix, B, Freeman, BJC, Hes, R, and McConichie, A: *Clinical performance and quality of life following Cadisc®-L total disc replacement: a prospective, non-randomised, multi-centre trial with 12 months follow-up*, ISASS Meeting, Barcelona, 2012

4.7 Mr. Dr. Hamid Afshar, statement available on request. Statement received via Scott Johnson, Technical Director, Ranier Technologies Ltd.

4.8 http://www.prnewswire.com/news-releases/ranier-technology-secures-gbp8m-funding-for-its-Cadisc®-replacement-spinal-discs-56961057.html

4.9 https://www.orthoworld.com/knowent/ranier_091010.pdf

4.10a http://www.ranier.co.uk/index.php?public/news-and-events/news/view/ranier-technology-announces-approval-for-reimbursement-in-south-africa-for-Cadisc®-c-compliant-elastomeric-artificial-disc

4.10b http://www.ranier.co.uk/index.php?public/news-and-events/news/view/ranier-signs-with-distribution-partner-asdm-in-australia-for-lumbar-and-cervical-discs